Remarks

I. Double-Patenting Rejection

Claims 1-18 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of US Patent 6,258,595, in view of Fields et al, Virology, Vol. 2, 3rd edition, 1995, Philadelphia: Lippencott Willims and Wilkins; page 2183.

Applicants respectfully traverse this rejection.

The '595 patent claims a method of producing rAAV utilizing a host cell containing rep, cap and a hybrid Ad/AAV containing functional E1 and sufficient adenovirus sequences to permit replication of the hybrid virus. In contrast, the mammalian cell claimed and utilized in the present invention contains only minimal amount of adenoviral sequences required to express E1a, E1b, and E2a gene product.

In addition, the '595 patent is effective as prior art only as of September 23, 1999. Therefore, it is not available as prior art against the presently claimed subject matter, which is entitled to a defensive §102(e) date of March 20, 1998, and its combination with Fields is improper.

Applicants request that this rejection be reconsidered and withdrawn.

II. Claim Rejections - 35 USC §102

Claims 1, 2, 9, 11, 14, 15 and 21-24 are rejected under 35 USC §102(e) as being anticipated by Wilson et al, US Patent 5,856,152.

Applicants respectfully traverse the rejection.

The '152 patent refers to the use of a hybrid Ad/AAV vector for production of rAAV. A hybrid Ad/AAV virus contains, at least the adenoviral 5' and 3' inverted terminal repeats (ITRs) and the native 5' packaging/enhancer domain, that contains sequences necessary for packaging linear Ad genomes and enhancer elements for the E1 promoter. As set forth in column 6, lines 12 - 29, based on the numbering of the human Ad5 genome, this includes adenoviral 5' sequences corresponding to about bp

1 to about 360 of the human Ad5 genome (mu 0-1.) The hybrid Ad/AAV further contains the 3' adenovirus ITR sequences, corresponding about base pairs 35,353 - end of the human Ad5 genome (mu 98.4-100). The hybrid Ad/AAV has an adenoviral capsid. The '152 patent teaches replication-incompetent hybrid Ad/AAV viruses, i.e., viruses from which the E1a and E1b functions have been eliminated. See, column 6, lines 52 - 55. However, other adenoviral sequences may be optionally present in the hybrid virus. Any missing adenoviral functions necessary for packaging of the hybrid Ad viral particle are supplied by a packaging cell line or a helper adenovirus [col. 7, lines 19 - 24].

In contrast, the cells of the invention contain only the minimum adenovirus DNA required to express an E1a gene product, an E1b gene product, and an E2a gene product. For example, based upon the teaching in the '152 patent, the E1a, E1b and E2a genes in the human Ad5 correspond to mu 1.3-4.5, mu 4.6-11.2 and mu 67.9 to 61.5, correspondingly. Thus, a portion of the 5' ITR sequences and all of the 3' ITR sequences are clearly excluded from the cells of the invention. Additionally, the cells of the invention do not contain any other adenoviral sequences, such as may be present in the hybrid Ad/AAV, or supplied by a packaging cell, of the '152 patent.

It is the inventors finding that only the E1a, E1b and E2a adenoviral gene functions are required to enable rAAV production which permitted this invention to be made. The prior art does not provide any host cell in which only these three adenoviral gene products are utilized for production of rAAV, in the absence of other adenoviral gene products. The advantage of the present invention are several. However, notably, no purification steps are required to remove helper virus or wild-type AAV because none is present in the host cells.

Applicants request reconsideration and withdrawal of the outstanding rejection.

III. Claim Rejections - 35 USC §103

Claims 10, 12 and 13 have been rejected under 35 USC §103(a) as being unpatentable over Wilson, '152, and further in view of Alkhatib et al, J. Virol., **62**(8):2718-27 (1988) and Fields et al, cited above. The same combination of art is applied to claims 3-8 and 16-20.

Applicants respectfully traverse this rejection.

The combined teachings of the cited art would teach against the claimed invention, which *avoids* the use of a helper virus.

In contrast, Wilson ('152) relies upon hybrid adenovirus/AAV viruses for transgene expression in cells.

Alkhatib refers to a hybrid adenovirus which contains an insert composed of the measles virus hemagglutinin in the native the E1a and E1b region in the Ad5 genome resulted in high titers of stable adenoviruses produced in 293 cells. As stated in the abstract, the 293 cells provide the missing E1 gene functions. However, 293 cells do not supply E2b function. Rather, these functions are provided by the recombinant adenovirus. This abstract does not teach or suggest any method useful to the production of a rAAV vector in the absence of helper virus.

Fields is relied upon for providing motivation to use E2a during production of rAAV. Fields neither teaches nor suggest a method for producing rAAV in the absence of helper virus.

Applicants believe that Alkhatib is non-analogous to the field of the present invention, which is directed towards production of rAAV and a cell useful therefor. However, even if this document is combined with the other cited prior art, there is no suggestion to provide a cell line containing only minimal E1a, E1b, and E2a gene functions and to produce rAAV *in the absence of a helper virus*.

Applicants request reconsideration and withdrawal of this rejection.

Applicants request that 1-18 be permitted to pass to issue.

The Director of the US Patent and Trademark Office is authorized to charge any deficiency in the fee associated with the filing of this paper to deposit account 08-3040.

Respectfully submitted,

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Appendix A

Marked-Up Copy of Pending Claims

1(Amended). A mammalian host cell useful for producing rAAV in the absence of a helper adenovirus comprising:

(a) a transgene under the control of regulatory sequences directing expression thereof and flanked by AAV [inverse] inverted terminal repeats;

(b) an AAV *rep* sequence and an AAV *cap* sequence under the control of regulatory sequences directing expression thereof; and

(c) adenovirus DNA sequences consisting of the minimum adenovirus DNA required to express an E1a gene product, an E1b gene product, and an E2a gene product.